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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,733	09/19/2003	Robert L. Bratzler	C1037.70051US00	6968
23628 7590 08/23/2007 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER ARCHIE, NINA	
			ART UNIT 1645	PAPER NUMBER
			MAIL DATE 08/23/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/666,733	Applicant(s) BRATZLER ET AL.	
	Examiner Nina A. Archie	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 62-69 is/are pending in the application.
- 4a) Of the above claim(s) 64 and 65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 62, 63 and 66-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/11/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Priority

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

2. The information disclosure statement filed on 4/11/2006 has been considered.
An initialed copy is enclosed.

Election/Restrictions

3. Applicant's election without traverse of Group 1 claims 62-69 is acknowledged.

Claims 64-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) in the reply filed on 6/1/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 62-63 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed toward a method to a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claim is not explicitly described in the specification, then the requirement for an adequate written description is met. To provide adequate written description and evidence of possession, the specification must provide sufficient description of the Claimed invention by i) actual reduction to practice or ii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis: i) Sufficient description of the claimed invention by actual reduction to practice: The specification gives general references of antibiotic resistance, wherein the specification lists many examples of different infection. (i.e. bacterial infection). Also the specification list several antibiotics and immunostimulatory acid molecules that could be use in the claimed method (see pgs. 12-14, 25-30, and 45-50). The specification does not teach any method of using of an oligonucleotide comprising an immunostimulatory nucleic acid to prevent antibiotic resistance. In the instant, the disclosure fails to evidence that Applicant is in possession of the claimed invention by actual reduction to practice. ii) Disclosure of relevant identifying characteristics: The disclosure fails to provide relevant identifying characteristics

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relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that prevents antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that the immunostimulatory nucleic acids must possess to prevent antibiotic resistance. As evidenced by Krieg, that teaches that each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies (see Krieg et al., CpG motif in bacterial DNA and their immune effects. *Annu. Rev. Immunol.*, 2002, Vol. 20, 709-760. (paragraph that bridge pages 716-717, in particular)). Additionally Mutwiri et al teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the in vitro immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif (see Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. *Veterinary Immunology and Immunopathology*, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90]). In the instant, the specification does not demonstrate that Applicant is in possession of an immunostimulatory nucleic acid to prevent antibiotic resistance therefore the skilled artisan cannot reasonably conclude or recognize that Applicant is in possession of the claimed invention at the time the invention was filed. Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

5. Claims 62-63 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention. The claims are drawn to a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The specification does not teach any method nor does the specification teach any of the myriad of possibilities of any immunostimulatory nucleic acid molecule having the claimed formula can be used to prevent antibiotic resistance, comprising: administering to a subject prior to, at the same

time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance.

The breadth of the claims. The product being used to administer to a subject (human or otherwise) stated in claim 62, an immunostimulatory nucleic acid is overly broad. The claims are drawn to a method for preventing any type of antibiotic resistance comprising administering to a subject (human or otherwise) prior, at the same time as or after the subject has received antibiotic therapy an effective amount of any immunostimulatory nucleic acid for preventing any type of antibiotic resistance. Therefore it is hard for one skilled in the art to determine if any immunostimulatory nucleic acid can be used for preventing any type of antibiotic resistance in a subject (human or otherwise). The quantity of experimentation required to practice the invention as claimed would require the determination of accessible target sites, modes of delivery and formulations, the route and time course of administration that encompass any immunostimulatory nucleic acid with limitations as discussed above to target appropriate cells and/or tissues in any and/or all organisms/subjects, and further whereby effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for preventing any type of antibiotic resistance in a subject comprising administering to a subject prior to, at the same time as, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance and since determination of these factors for a particular immunostimulatory nucleic acid for the particularly claimed conditions are not disclosed, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The state of the prior art. The state of the art is unpredictable with regard to preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. The art teaches that each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies

(see Krieg et al., CpG motif in bacterial DNA and their immune effects. *Annu. Rev. Immunol.*, 2002, Vol. 20, 709-760. (paragraph that bridge pages 716-717, in particular)). The art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the in vitro immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Mutwiri et al. also sets forth that in vitro observations do not accurately predict what happens in vivo (see Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. *Veterinary Immunology and Immunopathology*, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90). Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacing between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence. Moreover, the potential use of oligonucleotides containing immunostimulatory nucleic acids that prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al. Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza (see Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. *Curr. Top. Microbiol. Immunol.* 2000, Vol. 247, 23-40). Furthermore, major considerations for any nucleic acid therapy protocol involve issues such as the amount of oligonucleotide administered, what amount is considered therapeutically effective, the route and time course of administration, sites of administration. For example, Gura (*Science* vol. 270 p. 575-577, 1995, see p. 576 right column) teach that synthetic oligonucleotides have caused side

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effects in experimental animals and that when administered by one-time injection in high doses, several phosphorothioates drugs were lethal to some of the animals.

Furthermore, the oligonucleotides caused a transient decrease in two kinds of white blood cells as well as changes in blood pressure and heart rate. Such cardiovascular and other effects seen in animals can be minimized in patients using low doses of the compounds and administering then gradually by continuous intravenous injection.

Phosphorothioates have been found to accumulate in the liver, kidneys, and bone marrow of animals, although the long-term effects of this deposition are not clear (Gura). The art teaches that "immunomodulatory regimens offer an attractive approach as an adjunct modality for control of microbial diseases in the era of antibiotic resistance". The art teaches that there is a struggle to control infectious diseases and the immunostimulatory and immunosuppressive agents are capable of enhancing host defense mechanisms to provide protection against infections. The art teaches that when administering CpG ODN have given protection and partial protection against infections (see Masihi, K Expert Opin. Biol. Ther. July 2001, Vol. 1, No. 4, Pages 641-653 especially pg. 641-642, 646 and 648). The art teaches that "the spread of bacteria resistant to antimicrobial agents calls for population-wide treatment strategies to delay or reverse the trend toward antibiotic resistance, and that the treatment of all patients with a combination of antibiotics is in most cases the optimal strategy" (see Bonhoeffer et al 1997 Proc. Natl. Acad. Sci. Vol. 94 pgs. 12106-12111 in its entirety). Lastly there is no information on administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance. For the reasons set forth supra, the state of the art is unpredictable whether all immunostimulatory nucleic acids can prevent any type of antibiotic resistance in a subject.

Guidance in the specification/Working Examples. The specification does not contain any working examples that are directed to the claimed invention, a method for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an

immunostimulatory nucleic acid for preventing antibiotic resistance. The specification does not contain any working examples demonstrating that such immunostimulatory nucleic acids prevent any type of antibiotic resistance. The specification has not shown that the immunostimulatory nucleic acids contemplated by the claims prevent antibiotic resistance. The specification gives general references of antibiotic resistance, wherein the specification lists many examples of different infection. (i.e. bacterial infection). Also the specification list several antibiotics and immunostimulatory acid molecules that could be use in the claimed method (see pgs. 12-14, 25-30, and 45-50). The specification only speculates administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance oligonucleotides in a subject. It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that the claimed method would function in vivo or in vitro. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between in vitro or in vivo animal model assays and disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed in vivo method. As stated above, the specification has not provided much, if any, guidance or direction nor given any working examples relating to the claimed invention. In the instant, while the guidance or direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. Therefore, the specification fails to enable the claimed invention.

In conclusion, the claimed inventions are not enabled for preventing antibiotic resistance, comprising: administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of any immunostimulatory

nucleic acid for preventing antibiotic resistance. The product being used to administer to a subject stated in claim 62 is overly broad for preventing any type of antibiotic resistance. There is insufficient direction or guidance is presented in the specification using the claimed method for preventing antibiotic resistance. There are no working examples presented in the specification that teach the claimed method for preventing antibiotic resistance. The state of the art shows immunostimulatory nucleic acids must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Lastly there is no information on administering to a subject prior to, at the same time, or after the subject has received antibiotic therapy an effective amount of an immunostimulatory nucleic acid for preventing antibiotic resistance which renders the method for preventing antibiotic resistance unpredictable. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Status of the Claims

6. No claims are allowed.
Claims 62-63 and 66-69 are rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

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If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.




Nina A Archie

Examiner

GAU 1645

REM 3B31



MARK NAVARRO
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/666,733	Applicant(s)/Patent Under Reexamination BRATZLER ET AL.	
	Examiner Nina A. Archie	Art Unit 1645	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760.
	V	Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103.
	W	Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-4039
	X	Gura (Science vol. 270 p. 575-577, 1995, p. 576

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.